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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
BERCH, MARK L	

ART UNIT	PAPER NUMBER
1624	

NOTIFICATION DATE	DELIVERY MODE
01/06/2009	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

mailroom@bskb.com

Office Action Summary	Application No.	Applicant(s)	
	10/537,608	HOCEK ET AL.	
	Examiner	Art Unit	
	/Mark L. Berch/	1624	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *02 December 2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-3 and 5-13* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-3, 5-13* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *12/02/2008*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 12/02/2008 has been entered.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-3, 5-13 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

This case was filed without an adequate teaching of utility, because it is not specific enough. The specification teaches "pharmaceutical product such as an anticancer agent, an antiviral agent and the like, a production intermediate therefor". In view of the fact that there are hundreds of cancers, and thousands of viruses, this amounts to no more than a teaching for the public to figure out for themselves how to use. That will not suffice. As was stated in ***In re Gardner, Roe, and Willey***, 166 USPQ 138 at 141 (CCPA 1970), "In other

words, those skilled in the art, by investigations along the above lines, and by a great amount of work, can eventually find out how to use appellants' invention. But our view is that the law requires that the disclosure in the application shall inform them how to use, not how to find out how to use for themselves." It will take undue experimentation to figure out how to use.

Pursuant to ***In re Wands***, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988), one considers the following factors to determine whether undue experimentation is required: (A) The breadth of the claims; (B) The nature of the invention; (C) The state of the prior art; (D) The level of one of ordinary skill; (E) The level of predictability in the art; (F) The amount of direction provided by the inventor; (G) The existence of working examples; and (H) The quantity of experimentation needed to make or use the invention based on the content of the disclosure. Some experimentation is not fatal; the issue is whether the amount of experimentation is "undue"; see ***In re Vaeck***, 20 USPQ2d 1438, 1444.
The analysis is as follows:

(1) Breadth of claims.

(a) Scope of the compounds. Owing to the extremely wide range of R1, R2, R3 and R4 the A-linker, trillions of compounds are embraced.

(b) Scope of the diseases covered. The coverage of "anticancer ... antiviral "is immense. There are hundreds of types of cancers and tumors. They can occur in pretty much every part of the body. Here are some assorted categories:

A. CNS cancers cover a very diverse range of cancers in many categories and subcategories. There are an immense range of neuroepithelial tumors. Gliomas, the most common subtype of primary brain tumors, most of which are aggressive, highly invasive, and neurologically

destructive tumors are considered to be among the deadliest of human cancers. These are any cancers which show evidence (histological, immunohistochemical, ultrastructural) of glial differentiation These fall mostly into five categories. There are the astrocytic tumors (Astrocytomas): Pilocytic astrocytoma (including juvenile pilocytic astrocytoma, JPA, and pediatric Optic Nerve Glioma) Diffuse astrocytomas (including Fibrillary astrocytomas, Protoplasmic astrocytomas and Gemistocytic astrocytomas), Anaplastic astrocytomas (including adult Optic Nerve Glioma), Glioblastoma multiforme (GBM), gliosarcoma and giant cell glioblastoma, and Pleomorphic xanthoastrocytoma. GBM exists in two forms, primary and secondary, which have very different clinical histories and different genetics, but GBM is considered to be one clinical entity. Second, there are the oligodendroglial tumors (Oligodendrogliomas): Low grade Oligodendroglioma and Anaplastic Oligodendroglioma. Third, there is oligoastrocytomas ("mixed glioma"), a type of tumor with both astrocytoma & oligodendroglioma features. The fourth type is the Ependymomas, which are intracranial gliomas, including Papillary Ependymoma, Myxopapillary ependymoma, tanycytic ependymoma, Anaplastic ependymoma and subependymal giant-cell astrocytomas. A fifth type is the Gangliogliomas (glioneuronal tumors or glioneurocytic tumors), which have both glial and neuronal components, and are extremely varied, based in part on what types of glial and what types of neuronal components are present. These include Papillary Glioneuronal Tumor (PGNT), a range of Supratentorial gangliogliomas, assorted intramedullary spinal cord gangliogliomas, Pineal ganglioglioma, Hypothalamic ganglioglioma, cerebellar ganglioglioma, Ganglioglioma of the right optic tract, rosetted glioneuronal tumor ("glioneurocytic tumor with neuropil rosettes"), composite pleomorphic xanthoastrocytoma (PXA)-ganglioglioma, desmoplastic ganglioglioma (both infantile (DIG)

and non- infantile), Angioganglioglioma, and others. There are also some Glial tumors which do not comfortably fit into these five categories, notably Astroblastoma, Gliomatosis cerebri, and chordoid glioma, which is found solely in the Hypothalamus and Anterior Third Ventricle. Other neuroepithelial tumors include astrocytic tumors (e.g. astrocytomas) oligodendroglial tumors, Ependymal cell tumors (e.g. myxopapillary ependymoma), mixed gliomas (e.g. mixed oligoastrocytoma and ependymo-astrocytomas) tumors of the choroid plexus(Choroid plexus papilloma, Choroid plexus carcinoma), assorted neuronal and Neuroblastic tumors (e.g. gangliocytoma, central neurocytoma, dysembryoplastic neuroepithelial tumor, esthesioneuroblastoma, Olfactory neuroblastoma, Olfactory neuroepithelioma, and Neuroblastomas of the adrenal gland), pineal parenchyma tumors (e.g. pineocytoma, pineoblastoma, and Pineal parenchymal tumor of intermediate differentiation), embryonal tumors (e.g. medulloepithelioma, neuroblastoma, retinoblastoma, ependymoblastoma, Atypical teratoid/rhabdoid tumor, Desmoplastic medulloblastoma, Large cell medulloblastoma, Medullomyoblastoma, and Melanotic medulloblastoma) and others such as polar spongioblastoma and Gliomatosis cerebri. A second Division is tumors of the meninges. This includes tumors of the meningothelial cells, including Meningiomas (Meningothelial, Fibrous (fibroblastic), Transitional (mixed), Psammomatous, Angiomatous, Microcystic, Secretory, Lymphoplasmacyte-rich, Metaplastic, Clear cell, Chordoid, Atypical, Papillary, Rhabdoid, Anaplastic meningioma) and the non- Meningioma tumors of the meningothelial cells (Malignant fibrous histiocytoma, Leiomyoma, Leiomyosarcoma, Rhabdomyoma, Rhabdomyosarcoma, Chondroma, Chondrosarcoma, Osteoma, Osteosarcoma, Osteochondroma, Haemangioma, Epithelioid haemangioendothelioma, Haemangiopericytoma, Angiosarcoma, Kaposi

sarcoma). There are also Mesenchymal, non-meningothelial tumors (Lipomas, Angiolipoma, Hibernoma Liposarcoma, (intracranial)Solitary fibrous tumor, and Fibrosarcoma) as well as Primary melanocytic lesions (Diffuse melanocytosis, Melanocytoma, Malignant melanoma, and Meningeal melanomatosis). A third Division are the tumors of Cranial and Spinal Nerves. This includes Cellular schwannomas, Plexiform schwannomas and the Melanotic schwannomas (e.g. psammomatous melanotic schwannoma , Neuro-axial melanotic schwannoma, Dorsal dumb-bell melanotic schwannoma). There is also neurofibroma, Perineurioma (Intraneural and Soft tissue) and malignant peripheral nerve sheath tumor (MPNST), including Epithelioid, MPNST with divergent mesenchymal differentiation, and MPNST with epithelial differentiation. A fourth division are Germ Cell Tumors, including germinoma, embryonal carcinoma, yolk sac tumor, choriocarcinoma, and teratoma (Mature teratoma, Immature teratoma, and Teratoma with malignant transformation). A fifth division are the tumors of the Sellar Region, viz. pituitary adenoma, pituitary carcinoma, granular cell myoblastoma and craniopharyngiomas (Adamantinomatous and Papillary). Yet another division are local extensions from regional tumors, including paraganglioma, chodroma, chordoma, and chondrosarcoma. There are also Primitive Neuroectodermal Tumors (PNETs) including Medulloblastomas, medulloepitheliomas, ependymoblastomas and polar spongioblastomas. There are Vascular brain Tumors e.g. the hemangioblastomas, there is CNS Lymphoma (which can be primary or secondary) and Meningeal Carcinomatosis. There are Lymphoma AND Haemopoietic neoplasms including Malignant lymphomas (which can be primary or secondary), Plasmacytoma, and Granulocytic sarcoma. And there are many, many others.

B. Leukemia is any malignant neoplasm of the blood-forming tissues. Leukemia can arise from many different sources. These include viruses such as EBV, which causes Burkitt's lymphoma, and HTLV-1, linked to certain T cell leukemias. Others are linked to genetic disorders, such as Fanconi's anemia, which is a familial disorder, and Down's Syndrome. Other leukemias are caused by exposure to carcinogens such as benzene, and some are actually caused by treatment with other neoplastic agents. Still other leukemias arise from ionizing radiation, and many are idiopathic. Leukemias also differ greatly in the morphology, degree of differentiation, body location (e.g. bone marrow, lymphoid organs, etc.) There are dozens of leukemias. There are B-Cell Neoplasms such as B-cell prolymphocytic leukemia and Hairy cell leukemia (HCL, a chronic Lymphoid leukemia). There are T-Cell Neoplasms such as T-cell prolymphocytic leukemia, aggressive NK cell leukemia, adult T cell leukemia/lymphoma (ATLL), and T-cell granular Lymphocytic leukemia. There are different kinds of acute myeloid leukemias (undifferentiated AML, acute myeloblastic, acute myelomonocytic leukemia, acute monocytic leukemias, acute monoblastic, acute megakaryoblastic (AmegL), acute promyelocytic leukemia (APL), and erythroleukemia). There is also lymphoblastic leukemia, hypocellular acute myeloid leukemia, Ph-/BCR- myeloid leukemia, and acute basophilic leukemia. Chromic leukemias include chronic lymphocytic leukemia(CLL, which exists in a B-cell and a T-cell type), prolymphocytic leukemia(PLL), large granular lymphocytic leukemia (LGLL, which goes under several other names as well), chronic myelogenous leukemia(CML), chronic myelomonocytic leukemia (CMML), chronic neutrophilic leukemia, chronic eosinophilic leukemia(CEL), and many others.

C. Carcinomas of the Liver include Hepatocellular carcinoma, Combined hepatocellular cholangiocarcinoma, Cholangiocarcinoma (intrahepatic), Bile duct cystadenocarcinoma and Undifferentiated carcinoma of the liver. There are also two types of liver hemangioma: cavernous and hemangioendothelioma.

D. The main types of lung and pleural cancer are small cell (i.e. oat cell, including combined oat cell), adenocarcinomas, Bronchioloalveolar carcinomas (Nonmucinous, Mucinous, and Mixed mucinous and nonmucinous or indeterminate cell type), Acinar, Papillary carcinoma, Solid adenocarcinoma with mucin, Adenocarcinoma with mixed subtypes, Well-differentiated fetal adenocarcinoma, Mucinous (colloid) adenocarcinoma, Mucinous cystadenocarcinoma, Signet ring adenocarcinoma, and Clear cell adenocarcinoma), squamous cell (Papillary, Clear cell, Small cell and Basaloid), mesothelioma (including epithelioid, sarcomatoid, desmoplastic and biphasic) and Large Cell Carcinoma (which include Large-cell neuroendocrine carcinoma, Combined large-cell neuroendocrine carcinoma, Basaloid carcinoma, Clear cell carcinoma Lymphoepithelioma-like carcinoma, and Large-cell carcinoma with rhabdoid phenotype). In addition there are also the carcinomas with pleomorphic, sarcomatoid or sarcomatous elements, including Carcinomas with spindle and/or giant cells, Spindle cell carcinoma, Carcinosarcoma and Pulmonary blastoma. The non-small cell lung carcinomas also include Adenosquamous carcinoma, the Carcinoid tumor (both typical Carcinoid and atypical Carcinoid) as well as carcinomas of salivary-gland type, including mucoepidermoid carcinoma and adenoid cystic carcinoma. There are some soft tissue tumors including localized fibrous tumor (formerly called benign fibrous mesothelioma); epithelioid haemangioendothelioma; pleuropulmonary blastoma (which occurs three fairly different substituted-types); chondroma; calcifying fibrous

pseudotumor of the visceral pleura); congenital peribronchial myofibroblastic tumors, diffuse pulmonary lymphangiomyomatosis and desmoplastic round cell tumor. There are assorted bronchial adenomas (e.g. adenoid cystic carcinomas, mucoepidermoid carcinomas, mucous gland adenomas, and oncocytomatous bronchial mucous gland adenoma) as well as other adenomas, including papillary adenoma. There are some papillomas, including squamous cell papilloma and glandular papilloma. There is also malignant melanoma of the lung, Hamartoma, cylindroma (cylindroadenoma), some germ cell tumors, thymoma and sclerosing haemangioma and many others as well. Lung cancers are quite diverse. Thus, for example, oat cell carcinoma, Signet ring adenocarcinoma, pleuropulmonary blastoma, cylindroma, and malignant mesothelioma really have very little in common, other than being cancers of the lung.

E. Thyroid cancer comes in four forms: papillary thyroid cancer, follicular thyroid cancer, anaplastic thyroid cancer, and medullary thyroid cancer.

F. Carcinomas of the skin are the Basal cell carcinomas (BCC), including Superficial BCC, Nodular BCC (solid, adenoid cystic), Infiltrating BCC, Sclerosing BCC (desmoplastic, morpheic) , Fibroepithelial BCC, BCC with adnexal differentiation, Follicular BCC, Eccrine BCC, Basosquamous carcinoma, Keratotic BCC, Pigmented BCC, BCC in basal cell nevus syndrome, Micronodular BCC. Another important family is the Squamous cell carcinomas (SCC) which include Spindle cell (sarcomatoid) SCC, Acantholytic SCC, Verrucous SCC, SCC with horn formation, and Lymphoepithelial SCC, along with less well classified SCCs such as Papillary SCC, Clear cell SCC, Small cell SCC, Posttraumatic (e.g., Marjolin ulcer) and Metaplastic (carcinosarcomatous) SCC. Another family is the Eccrine carcinomas including Sclerosing sweat duct carcinoma (syringomatous carcinoma, microcystic adnexal

carcinoma), Malignant mixed tumor of the skin (malignant chondroid syringoma), Porocarcinoma, Malignant nodular hidradenoma, Malignant eccrine spiradenoma, Mucinous eccrine carcinoma, Adenoid cystic eccrine carcinoma, and Aggressive digital papillary adenoma/adenocarcinoma. Other carcinomas of the skin include Epidermal carcinomas, Paget disease, Mammary Paget disease, Merkel cell carcinoma (neuroendocrine cancer of the skin), Extramammary Paget disease Adnexal carcinomas, Apocrine carcinoma, Sebaceous carcinoma, Tricholemmocarcinoma and Malignant pilomatricoma (matrical carcinoma).

G. There are many types of colon cancers, and this category is rather diverse. Most are adenocarcinomas, either of the mucinous (colloid) type or the signet ring type. Less common colon cancers include squamous cell, neuroendocrine carcinomas, carcinomas of the scirrhous type, lymphomas, melanomas (which can be primary or metastatic), sarcomas (including fibrosarcomas and Leiomyosarcomas), and Carcinoid tumors.

H. Renal carcinomas comprise the papillary renal cell carcinoma (which has two subtypes, type 1 and type 2, with very different prognostic values), clear cell renal carcinoma, chromophobe renal carcinoma, collecting duct renal carcinoma, and some unclassified carcinomas (the Heidelberg classification system). Other kidney cancers include Transitional Cell Carcinoma, Wilms Tumor, malignant rhabdoid tumor of the kidney, renal melanoma, Primary Renal Non-Hodgkin's Lymphoma , Primary renal MALT lymphoma, Primary renal Hodgkin's lymphoma, secondary renal lymphomas, and renal sarcomas. In addition, there are the (usually) non-metastatic kidney tumors -- Renal adenomas, Oncocytomas, congenital mesoblastic nephroma, and Angiomyolipomas --- although the Angiomyolipomas often do not require treatment.

I. Prostate Cancer is not a single disease or group of very closely related disorders, but ranges over a very wide variety of cancer types. It embraces various adenocarcinomas of the prostate, including Prostatic Ductal Adenocarcinoma, adenocarcinoma with Paneth-like cells, Clear cell adenocarcinoma, Foamy gland adenocarcinoma, Adenocarcinoma of Cowper's glands, and Atrophic adenocarcinoma. It includes a huge variety of carcinomas, including mucinous carcinomas of the prostate, Prostatic carcinoma of xanthomatous type, signet ring cell carcinoma of the prostate, neuroendocrine small cell carcinoma of the prostate, and other small cell carcinomas of the prostate, Adenosquamous and Squamous Cell Carcinomas, Basaloid and Adenoid Cystic Carcinoma, Sarcomatoid carcinoma of the prostate, Lymphoepithelioma-like Carcinoma of the prostate, Urothelial (transitional Cell) Carcinoma (which can be primary in the prostate gland or represent secondary spread from the urinary bladder), Basaloid carcinoma, pseudohyperplastic carcinoma, and Primary carcinoma of the Seminal vesicles. There are also assorted sarcomas of the prostate, including Angiosarcoma, Embryonal rhabdomyosarcoma, Stromal sarcoma, Synovial sarcoma, Leiomyosarcoma, and chondrosarcoma of the prostate, which can be primary or secondary to the prostate. Also included is prostatic intraepithelial neoplasia (PIN), Phyllodes Tumor of the Prostate, Primitive peripheral neuroectodermal tumor (PNET) and Malignant fibrous histiocytoma. There are also lymphomas, which are usually secondary, but primary ones include Diffuse Large B-cell Lymphoma. The great majority of this list are not treatable with pharmaceuticals.

J. Penile carcinoma is usually a squamous cell carcinoma, but there is also Penile clear cell carcinoma and Sarcomatoid carcinoma.

K. The carcinomas of the extrahepatic bile ducts are of numerous types, including carcinoma in situ, Adenocarcinoma, Papillary adenocarcinoma, Adenocarcinoma (intestinal-type), Mucinous adenocarcinoma, Clear cell adenocarcinoma, Signet ring cell carcinoma, Adenosquamous carcinoma, Squamous cell carcinoma, Small cell carcinoma (oat cell carcinoma) and undifferentiated carcinoma of the extrahepatic bile ducts.

L. Breast cancers come in great variety. The most important category of breast cancers is the ductal cancers. These come in an assortment of types. Presently, these are divided into the following categories: Intraductal (in situ); Invasive with predominant intraductal component; Invasive, NOS; Comedo; Inflammatory (IBC); Medullary with lymphocytic infiltrate; Mucinous Carcinoma (colloid carcinoma); Papillary carcinoma; Scirrhous; Tubular; and Other. Another category is the Lobular breast cancers, which can be in situ, Invasive with predominant in situ component, and Invasive. There is Paget's disease of the Nipple, which can be also with intraductal carcinoma or with invasive ductal carcinoma. There is Adenomyoepithelioma , a dimorphic tumor characterized by the presence of both epithelial and myoepithelial cells. There is breast angiolipoma and spindle cell lipoma of the breast. There is lymphoma of the breast (which exists in both Non-Hodgkin's lymphoma of the breast and Hodgkin's disease of the breast forms). There are some sarcomas, including giant cell sarcoma of the breast, leiomyosarcoma of the breast, Angiosarcoma of the breast, cystosarcoma phylloides, and liposarcoma of the breast. There are carcinoid tumors which can be primary carcinoid tumors of the breast, or can arise from from nonmammary sources. There are breast salivary gland-like tumors, including acinic cell carcinoma (AcCC), oncocytic carcinoma (Mammary epithelial oncocytoma), and mucoepidermoid carcinoma (MEC). Other rare carcinomas include Spindle cell carcinoma

of the breast (SpCC), Squamous cell carcinoma of the breast, Secretory Carcinoma of the Breast (Juvenile secretory carcinoma), Metaplastic carcinoma of the breast (a heterogeneous group of invasive breast cancers including types with squamous differentiation and those with heterologous elements), Invasive Micropapillary Carcinoma of the Breast, Adenoid cystic carcinoma of the breast, cribriform carcinoma, Myofibroblastoma of the Breast (Benign spindle stromal tumor of the breast) and glycogen-rich clear cell carcinoma of the breast. There are numerous other rare breast cancers, including for example Fibromatosis of the breast (extra-abdominal desmoid), Angiomatosis of the Breast, and mammary hamartoma. There are also nonmammary tumors, primarily adenocarcinomas, that can metastasize to the breast including bronchogenic carcinomas, malignant melanomas (primary and secondary), rhabdomyosarcomas, malignant mesotheliomas, thyroid carcinomas, renal cell carcinomas, malignant lymphomas, and gastrointestinal carcinomas (including those from the stomach, pancreas, esophagus, and colon).

M. Ovarian cancers are a heterogeneous group of tumors. The most important are the epithelial tumors. These are themselves fairly diverse, the categories being Serous cystomas (Serous benign cystadenomas, Serous cystadenomas with proliferating activity of the epithelial cells and nuclear abnormalities but with no infiltrative destructive growth and Serous cystadenocarcinomas); Mucinous cystomas (divided the same three ways); Clear cell tumors (mesonephroid tumors, again divided the same way), Endometrioid tumors (similar to adenocarcinomas in the endometrium: Endometrioid benign cysts, Endometrioid tumors with proliferating activity of the epithelial cells and Endometrioid adenocarcinomas), mixed mesodermal (now considered to be carcinomas with areas of

sarcomatous differentiation), clear cell, transitional cell, and mixed epithelial. Second, there are the Granulosa-Stromal Cell Tumors. These include the Granulosa cell tumor (which exists in juvenile and adult forms) and the tumors in the thecoma-fibroma group. This includes thecoma-fibroma group typical thecoma and luteinized thecoma or "stromal Leydig cell tumor". This also includes fibroma, cellular fibroma, fibrosarcoma, stromal tumor with minor sex cord elements, sclerosing stromal tumor, signet ring cell stromal tumor and others. Third, there are the Sertoli-Leydig Cell Tumors and Androblastomas. These include the Sertoli cell tumor (tubular androblastoma), Sertoli-Leydig cell tumor , a poorly differentiated sarcomatoid, tumor and a Retiform tumor. Fourth, there are some miscellaneous Sex Cord Stromal Tumors, including Gynandroblastoma of the ovary (composed of sex cord and stromal cells of both ovarian and testicular types), Sex Cord Tumor with Annular Tubules, Stromal luteoma, and Leydig cell tumor)which comes in hilus and non-hilar types). Fifth, there are an assortment of Germ Cell Tumors. These include Dysgerminoma; Yolk Sac Tumors (Endodermal Sinus Tumor, and Polyvesicular vitelline tumor, Hepatoid and others); Embryonal Carcinoma; Polyembryoma; Choriocarcinoma and a wide variety of Teratomas. These tetromas include immature, cystic (dermoid cyst), retiform (homunculus), and Monodermal, including struma ovarii, carcinoid (insular and trabecular), struma carcinoid, mucinous carcinoid, neuroectodermal tumors, sebaceous tumors and others. Finally, there are an assortment of other tumors which do not fit into the above categories. There is Gonadoblastoma and Tumors of Rete Ovarii (which can be Adenomatoid tumor or a Mesothelioma). There are some tumors of Uncertain Origin, including Small cell carcinoma, tumors of probable Wolffian origin, a Hepatoid carcinoma and Oncocytoma. There are some Soft Tissue Tumors not Specific to

Ovary, and there are assorted malignant Lymphomas and Leukemias which land up in the ovaries.

N. Cervical cancers. There are many different categories and sub-categories of cervical cancers. The majority of cervical cancers are Squamous Cell Carcinomas. These come in numerous types: large cell nonkeratinizing type; large cell keratinizing type; Basaloid; Verrucous; Warty; Papillary; Lymphoepithelioma-like; and Squamotransitional, Early invasive (microinvasive) squamous cell carcinoma; Squamous intraepithelial neoplasia (including Cervical intraepithelial neoplasia and Squamous cell carcinoma in situ). There are also a variety of Adenocarcinomas, the most important of which are the Mucinous adenocarcinoma, which include the Endocervical, Intestinal, signet-ring cell, minimal deviation, and Villoglandular. There is also Endometrioid adenocarcinoma, clear cell adenocarcinoma, serous adenocarcinoma, Mesonephric adenocarcinoma, Early invasive adenocarcinoma, and Adenocarcinoma in situ. In addition, there are neuroendocrine carcinomas, divided into Small Cell, large cell, classical carcinoid and atypical carcinoid. Other epithelial tumors include Adenosquamous carcinoma, mixed Adenosquamous Carcinomas, which can be either well-differentiated or poorly differentiated, the latter including glassy cell carcinoma, adenoid cystic carcinoma, adenoid basal carcinoma and Undifferentiated carcinoma. There are also some mixed carcinoma with signet-ring cells, and other types of other poorly differentiated mixed carcinomas. This group includes tumors sometimes called apudomas or argyrophil cell carcinomas. There are also an assortment of Mesenchymal tumors of the cervix, including Leiomyosarcoma; Endometrioid stromal sarcoma, low grade; Undifferentiated endocervical sarcoma; Sarcoma botryoides; Alveolar soft part sarcoma, Angiosarcoma of the cervix, Malignant peripheral nerve sheath

tumor of the cervix; Cervical leiomyoma; and Rhabdomyoma of the cervix. There are also some mixed epithelial and mesenchymal tumors, including Carcinosarcoma (malignant müllerian mixed tumor), Adenosarcoma, Wilms tumor, typical and atypical Polypoid Adenomyoma, and Papillary adenofibroma of the cervix. There are also Melanocytic tumors, including primary malignant melanoma of the cervix and Blue naevus of the cervix. There are also germ cell type tumors, including Yolk sac tumor, Dermoid cyst, and Mature cystic teratoma of the cervix. There is also primary choriocarcinoma of the cervix, which does not fit well into any category. There are also cancers secondary to the cervix, which have spread from elsewhere.

O. Bladder cancers. Most cases of bladder cancers are transitional cell (urothelial) carcinoma, which includes non-invasive papillary urothelial carcinoma, Flat urothelial carcinoma in situ (CIS), Superficially invasive urothelial carcinoma, and muscle invasive tumors. Adenocarcinomas of the bladder include Primary Adenocarcinoma (urachal and non-urachal), Prostatic adenocarcinoma, Gastro-intestinal adenocarcinomas and Clear cell carcinoma. Squamous cell carcinomas include Verrucous carcinomas, and a secondary squamous cell carcinoma of the bladder, from the cervix. Small cell carcinomas include Primary small cell carcinoma of the bladder and the secondary small cell carcinoma ('reserve cell carcinoma') of the lung. Lymphomas include the primary lymphomas (Low grade B-cell lymphoma of MALT type, High grade B-cell lymphoma, and T-cell lymphoma), as well as secondary lymphomas, including mantle cell lymphomas. Melanomas include Primary Malignant melanoma of the bladder, and secondary ones. The sarcomas of the Bladder are Leiomyosarcoma, Osteosarcoma and Rhabdomyosarcoma. There is also a primary primitive neuroectodermal tumour (PNET) of the bladder, Paraganglioma (which

can metastasize), Nephrogenic adenoma, Metastatic renal cell carcinoma of the bladder, and both primary and secondary (from the uterus) Choriocarcinoma of the bladder.

P. Cancers of the Vulva are mostly Squamous carcinoma, but these also include Melanoma, Bartholin's Adenocarcinoma, Basal Cell carcinoma and some Sarcomas.

Q. Vaginal cancers are primarily Squamous Carcinoma, but some are Adenocarcinoma, Melanoma of the vagina; Sarcoma of the vagina, Bowen's disease and Germ Cell Tumors.

R. The most important of the cancers of the uterus are the Endometrial Carcinomas. The great majority of these are Endometrioid; others include Uterine Papillary Serous Tumor (UPST), Clear Cell Carcinoma, Mucinous and Squamous. Uterine Sarcomas include Smooth Muscle Tumors include leiomyoblastoma, clear cell leiomyoma, epithelioid leiomyoma, plexiform tumorlet, Intravenous leiomyomatosis, Benign metastasizing leiomyoma, Leiomyomatosis peritonealis disseminate and Leiomyosarcoma (LMS). Endometrial Tumors include Endometrial stromal nodule, Endolymphatic stromal myosis, (ESM) and Endometrial stromal sarcoma (ESS). There are the mixed tumors Müllerian adenosarcoma and Malignant mixed mesodermal tumors (MMMT). Other sarcomas are Rhabdosarcoma, Osteosarcoma, Chondrosarcoma nad Hemangiopericytoma. There are also uterine cancers which do not come from uterine cells themselves, but start in the tissue that begins to develop immediately after conception: Persistent gestational trophoblastic disease, choriocarcinoma and placental site trophoblastic tumors (PSTT).

S. There are several main types of stomach cancers, which are very different from each other. (1) Lymphomas of the stomach are cancers of the immune system tissue that are found in the wall of the stomach. These come in two main categories. One is the Non-

Hodgkin's lymphomas of the stomach, including MALT lymphoma, and assorted Large Cell Lymphoma of the Stomach such as anaplastic CD30 (Ki-1) positive large cell lymphoma (ALCL). The other is Hodgkin Lymphoma in the Stomach. These include both lymphomas which are primary to the stomach, and nodal lymphomas that have spread to the stomach from e.g. the spleen or liver and are thus secondary. There are Tertiary gastric lymphomas as well. (2) Gastric stromal tumors (GISTs) develop from the tissue of the stomach wall. There are an assortments of these; GISTs vary from cellular spindle cell tumors to epithelioid and pleomorphic ones. (3) Carcinoid tumors are tumors of hormone-producing cells of the stomach. These are classified into are classified into those that are associated with hypergastrinemic states (type 1, atrophic gastritis, pernicious anemia); Zollinger-Ellison syndrome [ZES] tumors (type 2), and tumors without hypergastrinemia (type 3 or sporadic). (4) Carcinoma of the Stomach exists in five types: papillary, tubular, mucinous, signet-ring cell adenocarcinoma and undifferentiated carcinoma. (5) Soft tissue sarcomas, most notably leiomyosarcoma of the stomach. There are other tumors as well, including Gastric Lipoma, gastric xanthelasma, and benign reactive lymphoid hyperplasia (pseudolymphoma).

In addition there are viruses. This is an immense category of diverse viruses.

Arenaviridae (the arenaviruses, Negative Stranded ssRNA) have considerable diversity. These are divided into two serogroups, the "Old World" and the "New World". The Old World includes the Ippy virus, Lassa virus (including different strains GA391 virus and Josiah virus), and Lymphocytic choriomeningitis virus (LCMV) (including several different strains of Armstrong virus as well as the WE virus). It also includes the Mobala virus and the Mopeia virus, each with multiple strains. The New World

arenaviruses include Amapari virus, Flexal virus, Guanarito virus, Junín virus, Latino virus, Machupo virus, Oliveros virus, Paraná virus, Pichinde virus, Pirital virus, Sabiá virus, Tacaribe virus, Tamiami virus, and Whitewater Arroyo virus. Again, many have multiple strains. These viruses are not necessarily closely related even within the same serogroup. For example, based on sequence data Pichinde virus appears to diverge quite extensively from the Tacaribe, Machupo, Junin, even though all 4 are New World. And the strains of LCMV (a virus actually found in Africa, Europe and the Americas) are only distantly related to the African viruses.

There is also the Filoviridae (Negative Stranded ssRNA), which consists of the Marburg virus (which has 6 different strains), and the Ebola virus (which has 4 different strains).

The Bunyaviridae Family (Negative Stranded ssRNA) is immense, with several genuses, including the Orthobunyavirus, Hantavirus, Nairovirus, and Phlebovirus. It includes the Acara virus, Akabane virus, Alajuela virus, San Juan virus, Anopheles B virus, Bakau virus, Batama virus, Birao virus, Bozo virus, Cache Valley virus, Fort Sherman virus, Germiston virus, Iaco virus, Mboke virus, Ngari virus, Northway virus, Bwamba virus, Capim virus, Caraparu virus, Catu virus, Estero Real virus, Gamboa virus, Guajara virus, Guama virus, Madrid virus, Manzanilla virus, Minatitlan virus, Nyando virus, Olifantsvlei virus, Oriboca virus, Sathuperi virus, Shuni virus, Tacaiuma virus, Wyeomyia virus, Kaeng Khoi virus, Andes virus, Bayou virus, Black Creek Canal virus, Cano Delgadito virus, Dobrava-Belgrade virus, Muleshoe virus, Puumala virus, Rio Mamore virus, Thailand virus, Topografov virus, Tula virus, Crimean-Congo hemorrhagic fever virus, Dugbe virus, Qalyub virus, Bujaru virus, Punta Toro virus, Rift Valley fever

virus, Salehebad virus, Sandfly fever Naples virus, Uukuniemi virus, Gabek Forest virus, Sandfly fever Sicilian virus and dozens more. Many of these have numerous different strains which have been identified. The family includes numerous viruses that are so poorly understood that it is impossible to place them in one of the above genuses, such as Bangui virus, Witwatersrand virus, and Kowanyama virus.

The human Flavivirus (Positive Stranded ssRNA Virus) are a diverse lot, including the Pestiviruses (such as Classical swine fever (CSF) and Bovine viral diarrhoea / Mucosal disease (BVD/MD)), Hepatitis C, Yellow fever virus, Gadgets Gully virus, Kadam virus, Kyasanur Forest disease virus, Langat virus, Omsk hemorrhagic fever virus, Powassan virus, Royal Farm virus, Tick-borne encephalitis virus, Meaban virus, Tyuleniy virus, Aroa virus, Dengue virus, Kedougou virus, Cacipacore virus, Koutango virus, Japanese encephalitis virus, Murray Valley encephalitis virus, St. Louis encephalitis virus, Usutu virus, West Nile virus, Kunjin virus, Ntaya virus, Uganda S virus, Apoi virus, Montana myotis leukoencephalitis virus, and many, many more.

The reoviruses (dsRNA Virus) have 12 genera. The Orthoreovirus includes the Mammalian orthoreovirus, Avian orthoreovirus, Nelson Bay orthoreovirus, and Baboon orthoreovirus, all with multiple strains, along with the Python orthoreovirus, Rattlesnake orthoreovirus Ndelle virus and the Duck reovirus. The Orbivirus includes the African horse sickness virus, Bluetongue virus, Epizootic hemorrhagic disease virus, Equine encephalosis virus, all with many strains, along with the Altamira virus (ALTV), Caninde virus (CANV), Changuinola virus (CGLV), Gurupi virus (GURV), Irituia virus (IRIV), Jamanxi virus (JAMV), Jari virus (JARIV), Monte Dourado virus (MDOV), Ourem virus (OURV), Purus virus (PURV), Saraca virus, Baku virus (BAKUV), Chenuda virus (CNUV),

Essaouira virus (ESSV), Huacho virus (HUAV), Kala Iris (KIRV), Mono Lake virus (MLV), Sixgun city virus (SCV), Chobar Gorge virus (CGV), Fomede virus, Acado virus (ACDV), Corriparta virus CS109, Corriparta virus V654, Corriparta virus V370, Jacareacanga virus, Above Maiden virus, Arbroath virus (ABRV), Bauline virus (BAUV), Broadhaven virus (BRDV), Cape Wrath virus (CWV), Colony virus (COYV), Colony B North virus, Ellidaey virus (ELLV), Foula virus (FOUV), Great Island virus (GIV), Great Saltee Island virus (GSIV), Grimsey virus (GSYV), Inner Farne virus (INFV), Kemerovo virus (KEMV), Kenai virus (KENV), Kharagysh virus (KHAV), Lipovnik virus (LIPV), Lundy virus (LUNV), Maiden virus (MDNV), Mill Door virus (MDRV), Mykines virus (MYKV), North Clett virus (NCLV), North End virus (NEDV), Nugget virus (NUGV), Okhotskiy virus (OKHV), Poovoot virus (POOV), Rost Island virus (RSTV), St Abb's Head virus (SAHV), Shiant Islands virus (SHIV), Thormodseyjarlettur virus (THRV), Tillamook virus, Tindholmur virus (TDMV), Tribec virus (TRBV), Vearoy virus (VAEV), Wexford virus (WEXV), Yaquina Head virus (YHV), Wexford virus (WEXV), Lebombo virus 1 (LEBV), Orungo virus, Abadina virus (ABAV), Bunyip creek virus (BCV), CSIRO village virus (CVGV), D'Aguilar virus (DAGV), Kasba virus (KASV), Chuzan virus, Kindia virus (KINV), Marrakai virus (MARV), Nyabira virus (NYAV),Palyam virus (PALV), Petevo virus (PETV), Vellore virus, Llano Seco virus (LLSV), Minnal virus (MINV), Netivot virus (NETV), Umatilla virus (UMAV), Wad Medani virus, Seletar virus, Mudjinbarry virus (MUDV), Wallal virus (WALV), Wallal K virus, Mitchell River virus (MRV), Warrego virus (WARV), Warrego K virus, Paroo River virus (PRV), Picola virus (PIAV), Wongorr virus MRM1343, Wongorr virus CS131, Wongorr virus V195, Wongorr virus V199, Wongorr virus V595, Wongorr virus V1447, Andasibe virus, Codajas virus (COV), Ife virus (IFEV), Itupiranga

virus (ITUV), Japanaut virus (JAPV), Kammavanpettai virus (KMPV), Lake Clarendon virus (LCV), Matucare virus (MATV), Peruvian horse virus (PHV), Peruvian rodent virus (PC21) (PRV), St Croix River virus (SCRV), Tembe virus (TMEV) and Tracambe virus. The rotoviruses are devided in to 7 species, Rotovirus A-G. The Coltivirus has Colorado tick fever virus and Eyach virus. The Seadornavirus has the Banna virus, Kadipo virus, each with many strains. The Aquareovirus has American oyster reovirus, Angel fish reovirus, Atlantic salmon reovirus, Chinook salmon reovirus DRC, Chum salmon reovirus CS, Masou salmon reovirus, Smelt reovirus, Striped bass reovirus, Chinook salmon reovirus B, Chinook salmon reovirus ICR, Chinook salmon reovirus LBS, Chinook salmon reovirus YRC, Coho salmon reovirus CSR, Coho salmon reovirus ELC, Coho salmon reovirus SCS, Golden shiner reovirus, Grass carp reovirus, Aquareovirus D (ARV-D), Channel catfish reovirus, Aquareovirus E (ARV-E), Turbot reovirus, Aquareovirus F (ARV-F), Chum salmon reovirus PSR, Coho salmon reovirus SSR, Chub reovirus (CHRV), Goldenide reovirus (GIRV), Hard clam reovirus (HCRV), Landlocked salmon reovirus (LSRV), and Tench reovirus (TNRV). The Cypoviruses include Bombyx mori cypovirus 1, Dendrolimus punctatus cypovirus 1, Dendrolimus spectabilis cypovirus 1, Lymantria dispar cypovirus 1, Aporophyla lutulenta cypovirus 10, Heliothis armigera cypovirus 11, Heliothis zea cypovirus 11, Lymantria dispar cypovirus 11, Mamestra brassicae cypovirus 11, Pectinophora gossypiella cypovirus 11, Pseudaletia unipuncta cypovirus 11, Spodoptera exempta cypovirus 11, Spodoptera exigua cypovirus 11, Autographa gamma cypovirus 12, Mamestra brassicae cypovirus 12, Pieris rapae cypovirus 12, Spodoptera exempta cypovirus 12, Polistes hebraeus cypovirus 13, Heliotis armigera cypovirus 14 A strain, Lymantria dispar cypovirus 14, Trichoplusia ni cypovirus 15, Trichoplusia ni cytoplasmic polyhedrosis

virus 15, Choristoneura fumiferana cypovirus 16, Aglais urticae cypovirus 2, Agraulis vanillae cypovirus 2, Arctia caja cypovirus 2, Arctia villica cypovirus 2, Boliria dia cypovirus 2, Boloria dia cypovirus 2, Dasychira pudibunda cypovirus 2, Eriogaster lanestris cypovirus 2, Hyloicus pinastri cypovirus 2, Inachis io cypovirus 2, Lacanobia oleracea cypovirus 2, Malacosoma neustria cypovirus 2, Mamestra brassicae cypovirus 2, Operophtera brumata cypovirus 2, Papilio machaon cypovirus 2, Phalera bucephala cypovirus 2, Pieris rapae cypovirus 2, Anaitis plagiata cypovirus 3, Arctia caja cypovirus 3, Danaus plexippus cypovirus 3, Gonometa rufibrunnea cypovirus 3, Malacosoma neustria cypovirus 3, Operophtera brumata cypovirus 3, Phlogophera meticulosa cypovirus 3, Pieris rapae cypovirus 3, Spodoptera exempta cypovirus 3, Actias selene cypovirus 4, Antheraea assamensis cypovirus 4, Antheraea mylitta cypovirus 4, Antheraea pernyi cypovirus 4, Antheraea proylei cypovirus 4, Euxoa scandens cypovirus 5, Heliothis armigera cypovirus 5, Orgyia pseudotsugata cypovirus 5, Spodoptera exempta cypovirus 5, Trichoplusia ni cypovirus 5, Aglais urticae cypovirus 6, Agrochola helvolva cypovirus 6, Agrochola lychnidis cypovirus 6, Anaitis plagiata cypovirus 6, Anti xanthomista cypovirus 6, Biston betularia cypovirus 6, Eriogaster lanestris cypovirus 6, Lasiocampa quercus cypovirus 6, Mamestra brassicae cypovirus 7, Noctua pronuba cypovirus 7, Abraxas grossulariata cypovirus 8, Heliothis armigera cypovirus 8, Malacosoma disstria cypovirus 8, Nudaurelia cytherea cypovirus 8, Phlogophora meticulosa cypovirus 8, Spodoptera exempta cypovirus 8, Agrotis segetum cypovirus 9, Heliothus armigera cypovirus B strain (HaCPV-B), Maruca vitrata cypovirus (A strain) (MvCPV-A), Maruca vitrata cypovirus (B strain) (MvCPV-B), and Plutella xylostella cypovirus (PxCPV). The Idnoreoviruses are Diadromus pulchellus idnoreovirus-1, Diadromus pulchellus reovirus, Hyposoter exiguae idnoreovirus-2,

Hyposoter exiguae reovirus, Housefly virus, Musca domestica idnoreovirus-3, Musca domestica reovirus, Dacus oleae idnoreovirus-4, Dacus oleae reovirus, Ceratitis capitata I virus, Ceratitis capitata idnoreovirus-5, Ceratitis I virus, Drosophila F virus, Drosophila melanogaster idnoreovirus-5 and Drosophila S virus (DSV). The Fijiviruses include Galla fijiensis virus, Saccharum virus 2, Sugarcane Fiji disease virus, Garlic dwarf virus (GDV), Cereal tillering disease virus, Nanismo ruvido del mais, Mal de Rio Cuarto virus (MRCV), Nilaparvata lugens reovirus (NLRV), Arrhenatherum blue dwarf virus, Lolium enation virus, Pangola stunt virus (PaSV), and Rice black streak virus. The Phytoreoviruses include Ine ishuku-byo, Oryza virus 1, Rice mosaic virus, Rice stunt virus, Rice gall dwarf virus (RGDV), Aureogenus magnivena virus, Clover big vein virus, Clover wound tumor virus, Trifolium virus nervicrassans, Homalodisca vitripennis phytoreovirus, and Tobacco leaf enation phytoreovirus (TLEP). The Orzaviruses are the Echinochloa ragged stunt virus (ERSV) and the Rice ragged stunt virus (RRSV) which comes in many subtypes, and Cimex lactularius reovirus (CIRV), Macropipus depurator P reovirus (MdRV-P), Carcinus mediterraneus W2 virus (CcRV-W2), Porcelio dilatatus reovirus (PdRV), and Buthus occitanus reovirus. The Mycoreoviruses include Cryphonectria parasitica mycoreovirus-1, Cryphonectria parasitica reovirus 9B21, Cryphonectria parasitica mycoreovirus-2, Rosellinia anti-rot virus, and Rosellinia necatrix mycoreovirus-3/W370.

The retroviruses (ssRNA RT-Viruses) fall into seven different genuses. The first is Alpharetrovirus. These include the Avian leukosis virus (ALV) (which comes in two strains), Rous sarcoma virus (RSV), which has 3 strains, Avian carcinoma Mill Hill virus 2, Avian myeloblastosis virus, Avian myelocytomatosis virus 29, Avian sarcoma virus CT10, Fujinami sarcoma virus, UR2 sarcoma virus (also known as University of Rochester virus 2

and Avian sarcoma virus UR-2), and the Y73 sarcoma virus. The second genus is the Betaretrovirus. This include the Langur virus (LNGV), Mason-Pfizer monkey virus (which comes in 3 strains), Mouse mammary tumor virus, Ovine pulmonary adenocarcinoma virus, Jaagsiekte sheep retrovirus, and the Squirrel monkey retrovirus. The third genus is the Gammaretrovirus. This includes the Feline leukemia virus, Gibbon ape leukemia virus, Guinea pig type C oncovirus, Murine leukemia virus (which exists in at least 6 strains and isolates), Porcine type C oncovirus, Finkel-Biskis-Jinkins murine sarcoma, Gardner-Arnstein feline sarcoma virus, Hardy-Zuckerman feline sarcoma virus, Harvey murine sarcoma virus, Kirsten murine sarcoma virus, Moloney murine sarcoma virus, Snyder-Theilen feline sarcoma virus, Woolly monkey sarcoma virus, Viper retrovirus, Chick syncytial virus, Reticuloendotheliosis virus, and the Trager duck spleen necrosis virus. The fourth genus is the Deltaretrovirus. This includes the Bovine leukemia virus, Primate T-lymphotropic virus 1, Human T-lymphotropic virus 1 (HTLV-1), Simian T-lymphotropic virus 1 (STLV-1), Primate T-lymphotropic virus 2 (PTLV-2), Human T-lymphotropic virus 2 (HTLV-2), Simian T-lymphotropic virus 2 (STLV-2), and the Primate T-lymphotropic virus-3. The fifth genus is the Epsilonretrovirus. These include the Walleye dermal sarcoma virus, Walleye epidermal hyperplasia virus type 1, Walleye epidermal hyperplasia virus type 2, Perch hyperplasia virus, and the Snakehead retrovirus. The sixth Genus is the Lentivirus. This includes Bovine immunodeficiency virus, Equine infectious anemia virus, Feline immunodeficiency virus, Feline immunodeficiency virus (Oma), Puma lentivirus, Caprine arthritis encephalitis virus, Visna/maedi virus (which comes in 3 strains), Human immunodeficiency virus 1 (HIV-1, which comes is many strains), HIV-2, HIV-3, and Simian immunodeficiency virus (SIV) which comes in many strains, including

African green monkey, chimpanzee SIV, mandrill SIV and others. The seventh genus is the Spumavirus. This includes Bovine foamy virus, Chimpanzee foamy virus, Feline foamy virus, Simian foamy virus 1 and Simian foamy virus 3.

The above list is just a fraction of the actual list of known RNA viruses.

There is a very wide range of DNA viruses.

The papillomaviruses are devided in to 16 genera: Alphapapillomavirus (Human papillomavirus 2, Human papillomavirus 6, Human papillomavirus 7, Human papillomavirus 10, Human papillomavirus 16, Human papillomavirus 18, Human papillomavirus 26, Human papillomavirus 32, Human papillomavirus 34, Human papillomavirus 53, Human papillomavirus 54, Human papillomavirus 61, Human papillomavirus 71, Human papillomavirus cand90, Rhesus monkey papillomavirus 1); Betapapillomavirus (Human papillomavirus 5, Human papillomavirus 9, Human papillomavirus 49, Human papillomavirus cand92, Human papillomavirus cand96); Gammapapillomavirus (Human papillomavirus 4, Human papillomavirus 48, Human papillomavirus 50, Human papillomavirus 60, Human papillomavirus 88); Deltapapillomavirus (Bovine papillomavirus 1, Deer papillomavirus, European elk papillomavirus, Ovine papillomavirus 1); ,Epsilonpapillomavirus (Bovine papillomavirus 5); Zetapapillomavirus (Equine papillomavirus 1); Etapapillomavirus (Fringilla coelebs papillomavirus); Thetapapillomavirus (Psittacus erithacus timneh papillomavirus); Iotapapillomavirus (Mastomys natalensis papillomavirus); Kappapapillomavirus (Cottontail rabbit papillomavirus, Rabbit oral papillomavirus); Lambdapapillomavirus (Canine oral papillomavirus, (Feline papillomavirus); Mupapillomavirus (Human papillomavirus 1, Human papillomavirus 63); Nupapillomavirus (Human papillomavirus

41); Xipapillomavirus(Bovine papillomavirus 3); Omicronpapillomavirus (Phocoena spinipinnis papillomavirus); and Pipapillomavirus (Hamster oral papillomavirus).

The polyomviruses consist of the African green monkey polyomavirus, Baboon polyomavirus 2, BK polyomavirus, Bovine polyomavirus, Budgerigar fledgling disease polyomavirus, Hamster polyomavirus, KI Polyomavirus, WU Polyomavirus, Merkel cell polyomavirus , JC polyomavirus, Murine pneumotropic virus, Murine polyomavirus, Rabbit kidney vacuolating virus, Simian virus 12, and Simian virus 40.

The Herpes viruses are mostly assigned to three subfamilies. Subfamily Alphaherpesvirinae: Ateline herpesvirus 1, Bovine herpesvirus 2, Cercopithecine herpesvirus 1, Cercopithecine herpesvirus 2, Cercopithecine herpesvirus 16, Human herpesvirus 1, Human herpesvirus 2, Macropodid herpesvirus 1, Macropodid herpesvirus 2, Saimiriine herpesvirus 1, Bovine herpesvirus 1, Bovine herpesvirus 5, Bubaline herpesvirus 1, Canid herpesvirus 1, Caprine herpesvirus 1
Cercopithecine herpesvirus 9, Cervid herpesvirus 1, Cervid herpesvirus 2, Equid herpesvirus 1, Equid herpesvirus 3, Equid herpesvirus 4, Equid herpesvirus 8
Equid herpesvirus 9, Felid herpesvirus 1, Human herpesvirus 3, Phocid herpesvirus 1, Suid herpesvirus 1, Gallid herpesvirus 2, Gallid herpesvirus 3, Meleagrid herpesvirus 1, Gallid herpesvirus 1, and Psittacid herpesvirus 1. Subfamily Betaherpesvirinae: Cercopithecine herpesvirus 5, Cercopithecine herpesvirus 8, Human herpesvirus 5, Pongine herpesvirus 4, Murid herpesvirus 1, Murid herpesvirus 2, Human herpesvirus 6, Human herpesvirus 7, Caviid herpesvirus 2, and Tupaiid herpesvirus 1. Subfamily Gammaherpesvirinae: Callitrichine herpesvirus 3, Circopithecine herpesvirus 12, Cercopithecine herpesvirus 14, Cercopithecine herpesvirus 15, Human herpesvirus 4, Pongine herpesvirus 1, Pongine

herpesvirus 2, Pongine herpesvirus 3, Alcelaphine herpesvirus 1, Alcelaphine herpesvirus 2, Ateline herpesvirus 2, Bovine herpesvirus 4
Cercopithecine herpesvirus 17, Equid herpesvirus 2, Equid herpesvirus 5, Equid herpesvirus 7, Hippotragine herpesvirus 1, Human herpesvirus 8, Murid herpesvirus 4, Mustelid herpesvirus 1, Ovine herpesvirus 2, Saimiriine herpesvirus 2 and Callitrichine herpesvirus 1. In addition, there are a number of Herpesviruses which have not been assigned to one of the three subfamilies: Ictalurid herpesvirus 1, Acipenserid herpesvirus 1, Acipenserid herpesvirus 2, Acciptrid herpesvirus 1, Anatid herpesvirus 1 and Anguillid herpesvirus 1.

The Herpes viruses show considerable diversity. For example, the Alphaherpesvirinae have a short reproductive cycle, and are neurotropic, whereas the Betaherpesvirinae have a long reproductive cycle and are lymphotropic. Herpesviruses are similar in terms of virion structure but are widely separated in terms of genomic sequence and proteins. They have no common antigens. Their shape is unusually complex.

The adenoviruses are devided into four genera: Mastadenovirus: Bovine adenovirus A, Bovine adenovirus B, Bovine adenovirus C, Canine adenovirus, Equine adenovirus A, Equine adenovirus B, Human adenovirus A, Human adenovirus B, Human adenovirus C, Human adenovirus D, Human adenovirus E, Human adenovirus F, Murine adenovirus A, Ovine adenovirus A, Ovine adenovirus B, Porcine adenovirus A, Porcine adenovirus B, Porcine adenovirus C, and Tree shrew adenovirus; Aviadenovirus: Fowl adenovirus A, Fowl adenovirus B, Fowl adenovirus C, Fowl adenovirus D, Fowl adenovirus E, and Goose

adenovirus; Atadenovirus: Bovine adenovirus D, Duck adenovirus A, Ovine adenovirus D, and Possum adenovirus; and Siadenovirus: Frog adenovirus, Turkey adenovirus A.

In addition, there are further adenovirus serotypes. Thus, while there are 6 species of human adenovirus (Human adenovirus A-F), there are 51 immunologically distinct human adenovirus serotypes that can cause human infections ranging from respiratory disease, to conjunctivitis to gastroenteritis and possibly, obesity.

The Parvovirinae viruses are devided into five genera: Parvovirus: Chicken parvovirus, Feline panleukopenia virus, H-1 parvovirus, HB parvovirus, Kilham rat virus, Lapine parvovirus, LuIII virus, Minute virus of mice, Mouse parvovirus 1, Porcine parvovirus, RT parvovirus, Tumor virus X, Erythrovirus, Human parvovirus B19, Pig-tailed macaque parvovirus, Rhesus macaque parvovirus, and Simian parvovirus. Dependovirus: Adeno-associated virus 1, Adeno-associated virus 2, Adeno-associated virus 3, Adeno-associated virus 4, Adeno-associated virus 5, Avian adeno-associated virus, Bovine adeno-associated virus, Canine adeno-associated virus, Duck parvovirus, Equine adeno-associated virus, Goose parvovirus, and Ovine adeno-associated virus. Amdovirus: Aleutian mink disease virus. Bocavirus: Bovine parvovirus, and Canine minute virus.

The Circovirus are Beak and feather disease virus, Canary circovirus, Goose circovirus, Pigeon circovirus, Porcine circovirus – 1, Porcine circovirus - 2 and Chicken anemia virus.

The hepadnaviruses consist of Ground squirrel hepatitis virus, Hepatitis B virus, Woodchuck hepatitis virus, Woolly monkey hepatitis B virus, Duck hepatitis B virus and Heron hepatitis B virus.

There are many other DNA viruses as well.

The specification also refers to use as an intermediate, but since the specification does not say what the compounds are an intermediate for, this is of no value.

(2) The nature of the invention and predictability in the art: With specific reference to cancer, ***Ex parte Kranz***, 19 USPQ2d 1216, 1219 notes the "general unpredictability of the field [of] ...anti-cancer treatment." ***In re Application of Hozumi et al.***, 226 USPQ 353 notes the "fact that the art of cancer chemotherapy is highly unpredictable". More generally, the invention is directed toward medicine and is therefore physiological in nature. It is well established that "the scope of enablement varies inversely with the degree of unpredictability of the factors involved," and physiological activity is generally considered to be an unpredictable factor. See ***In re Fisher***, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970).

(3) Direction or Guidance: None is provided. No cancer or virus is named. The dosage range information is entirely absent.

(4) State of the Prior Art: The claimed compounds are novel, or are anticipated only by species having no utility. Moreover, the compound tend to have structural features not generally present in antiviral or anticancer compounds. For example, R4 is H or organic group. The simplest organic groups are alkyls. So far as the examiner is aware, there is no effective antiviral or anticancer purine with this 9-alkyl feature. The simplest linker at the 6-position would be an alkylene chain (or a bond), giving an alkanoic acid or ester substituted by an amino group at the 6-position. So far as the examiner is aware, there are no antiviral or anticancer purines with an alkanoic acid or ester either unsubstituted or substituted by anything at the 6-position. Similarly, the examiner notes that R2 and R2 can be alkyl. Again, compounds with such features are simply not seen. Indeed, there are

a very small number of purines which have actually been shown to be effective antivirals. So far as the examiner is aware, not a single one has a Carbon atom attached to the 6-position.

(5) Working Examples: There are none. There is no biological data of any kind.

(6) Skill of those in the art: The prior art knows that there never has been a compound capable of treating cancer generally. "The cancer therapy art remains highly unpredictable, and no example exists for efficacy of a single product against tumors generally." (<http://www.uspto.gov/web/offices/pac/dapp/1pecba.htm#7> ENABLEMENT DECISION TREE, Example F, situation 1). A similar statement appears at ***In re Application of Hozumi et al.***, 226 USPQ 353: "In spite of the vast expenditure of human and capital resources in recent years, no one drug has been found which is effective in treating all types of cancer. Cancer is not a simple disease, nor is it even a single disease, but a complex of a multitude of different entities, each behaving in a different way". There are compounds that treat a modest range of cancers, but no one has ever been able to figure out how to get a compound to be effective against cancer generally, or even a majority of cancers. Thus, the existence of such a "silver bullet" is contrary to our present understanding in oncology. This is because it is now understood that there is no "master switch" for cancers generally; cancers arise from a bewildering variety of differing mechanisms. Even the most broadly effective antitumor agents are only effective against a small fraction of the vast number of different cancers known. This is true in part because cancers arise from a wide variety of sources, such as viruses (an estimated at least 20% are of viral origin e.g. EBV, Hepatitis B and C, HHV-8, HTLV-1 and other retroviruses, and

quite possibly Merkel cell polyomavirus), exposure to chemicals such as tobacco tars, genetic disorders (e.g. Tuberous Sclerosis), excess alcohol consumption (which causes hepatic cirrhosis, an important cause of HCC), ionizing radiation, and a wide variety of failures of the body's cell growth regulatory mechanisms.

Different types of cancers affect different organs and have different methods of growth and harm to the body, and different vulnerabilities. Cancers that affect just a certain type of structure can be quite varied. Fibromas for example include Infantile myofibromatosis, Fibrous hamartoma of infancy. Juvenile hyaline fibromatoses. Infantile digital fibromatoses. Calcifying aponeurotic fibromas. Giant cell fibroblastoma. Ovarian fibroma, Dermatofibroma, myofibroma, myofibromatosis, desmoplastic fibroma, neurofibroma, peripheral odontogenic fibroma, peripheral ossifying fibroma, giant cell fibroma, Chondromyxoid Fibroma, Oral Neurofibroma, Juvenile aponeurotic fibroma (JAF), aggressive infantile fibromatosis (AIF), omental fibroma, Perifollicular fibroma, ameloblastic fibroma, Premalignant Fibroepithelial Tumor (Pinkus Tumor), Periungual fibroma (Koenen tumor), desmoid tumor, tracheal fibroma and many others. Since it is beyond the skill of oncologists today to get an agent to be effective against cancers generally, evidence that the level of skill in this art is low relative to the difficulty of such a task. The skill thus depends on the particular cancer involved. There are a few cancers where the skill level is high and there are multiple successful chemotherapeutic treatments.

One skilled in the art knows that chemotherapy of brain tumors is especially difficult. This is because 1) the blood-brain barrier, which is often intact in parts or all of a brain tumor, will block out many drugs, as it is the purpose of the blood-brain barrier to

protect the brain from alien chemicals, and 2) CNS tumors are characterized by marked heterogeneity, which greatly decreases vulnerability to chemotherapy. As a result, many categories of CNS tumors simply have no chemotherapy available. These include, generally, hemangiomas and hemangioblastomas, meningiomas, craniopharyngiomas, acoustic neuromas, pituitary adenomas, optic nerve gliomas, glomus jugulare tumors and chordomas, to name just some. With regard to gliomas, GBM is considered untreatable; no effective agents have emerged for the treatment of GBM, despite 20 years of enrolling patients in clinical trials. It is radiation and surgery which are used for low grade gliomas (e.g. Pilocytic astrocytoma and Diffuse astrocytomas), as no drug has been found effective. There is no drug treatment established as effective for optic nerve gliomas or gangliogliomas. Indeed, very few gliomas of any type are treated with pharmaceuticals; it is one of the categories of cancer that is the least responsive to drugs.

Cartilage tumors do not respond to chemotherapy, nor do Cancerous teratomas. Of the thyroid cancers, only one (anaplastic thyroid cancer) can be treated with anticancer agents. The other are treated with radioactivity, surgery, or thyroid suppression hormones. Lymphomas of the stomach are not commonly treated with ordinary anti-cancer agents, but instead, surgery or radiation and antibiotic therapy (e.g. amoxicillin, metronidazole, bismuth, omeprazole) are the Primary Treatments. Neuroendocrine tumors of the cervix generally do not respond to chemotherapy. A number of sarcomas, including Alveolar soft part sarcoma (ASPS), retroperitoneal sarcoma, most liposarcomas, and the assorted chondrosarcomas, are generally considered not to respond to chemotherapy; no chemotherapeutic agent has been established as effective. Aggressive NK cell leukemia is considered to be untreatable with pharmaceuticals. Many cerebral metastases, such as

those from non-small-cell lung cancer and melanoma, are not chemosensitive and will not respond to chemotherapy. Hepatocellular Carcinoma (HCC or hepatoma) is, in humans, possibly the most prevalent solid tumor and in certain parts of the world is the most common cancer.

It is important to note that tumors can need to be treated quite different even though they are tumors of the same organ. For example, the drugs used most often to treat Wilms tumor, the most common malignant tumor of the kidneys in children, are actinomycin D and vincristine. Such drugs are never used with clear cell renal carcinoma, which is treated, although without much success, with Immunotherapy using the cytokines interleukin-2 and interferon-alpha. However, such immunotherapy has never been established as effective in non- clear cell RCC forms such as papillary renal cell carcinoma. Despite strenuous efforts over a period of decades, no chemotherapeutic agent has ever been found effective against this cancer.

Much the same is true for viruses. One of ordinary skill in the art knows that these viruses, and their polymerases, are quite diverse. Viruses exhibit huge variations in their nature. Some virions consist of just a capsid, some of just a nucleocapsid. Some consists of an envelope and a nucleocapsid, and some of an envelope and a core. Some virions consist of an envelope, a nucleocapsid, and a nucleoid. Other virions consist of an envelope, a matrix protein, a nucleoprotein complex, a nucleocapsid, and a polymerase complex, and there are many other forms as well.

The nucleic acids vary considerably as well. In some, the genome is segmented and consists of three segments of circular, negative-sense, single-stranded and double-stranded RNA. In others, the genome is segmented and consists of eight segments of, negative-sense,

single-stranded RNA. In others, the genome is not segmented and contains a single molecule of linear positive-sense, single-stranded RNA, or linear double-stranded RNA. In still others, the genome is monomeric, segmented and consists of ten segments of linear double-stranded RNA. In others, the genome consists of three segments of linear, double - stranded RNA. Some genomes are dimeric. Some have non-genomic nucleic acid, some don't. There are many, many other forms. There can be great variation even in the number of nucleotides present.

The viral polymerases are diverse, and include some forms which can use RNA as a template instead of DNA, a type known as RNA dependent RNA polymerases (RDRPs). This type is seen in e.g. some positive strand RNA viruses. The best known RDRPs are polioviral 3Dpol, vesicular stomatitis virus L, and hepatitus C virus NS5b protein. Unlike in the bacterial area, broad based antivirals are unknown. Even a viral agent against a family such as the Arenaviridae or the Bunyaviridae is unknown; these viruses are simply too diverse. The vast majority of RNA viruses have no effective antiviral treatment.

DNA viruses are even more difficult to treat than RNA viruses. Important human DNA viruses such as HHV-8 (causative agent for Kaposi's Sarcoma, the most important AIDS-related neoplasm), Epstein-Barr virus (linked to infectious mononucleosis; nasopharygeal carcinoma; several lymphomas; some thymomas; hairy leukoplakia, and other disorders) and Human parvovirus B19 (which causes things ranging from Fifth disease to acute, severe anemia) are untreatable. No antiviral agent has ever been found effective against any human adenovirus. The human polyomaviruses (BK, KI, WU, JC and

Merkel cell polyomavirus), which are causative agents for things like progressive multifocal leukoencephalopathy and Merkel cell carcinoma, have no effective antiviral treatment. (7) The quantity of experimentation needed: Given the fact that historically the development of new cancer and anti-viral drugs has been difficult and time consuming, and especially in view of factors 1, 3, 6 and 4, the quantity of experimentation needed is expected to be great, because the specification lacks any proper guidance as to what sort of cancer or virus the compounds can be used for.

MPEP 2164.01(a) states, "A conclusion of lack of enablement means that, based on the evidence regarding each of the above factors, the specification, at the time the application was filed, would not have taught one skilled in the art how to make and/or use the full scope of the claimed invention without undue experimentation. ***In re Wright***, 999 F.2d 1557,1562, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993)." That conclusion is clearly justified here.

The earlier traverse was unpersuasive. The examiner agrees that a single enabling utility is all that compounds need. That, however, is lacking. What the specification teaches will, for reasons set forth above, require undue experimentation. This specification is a good example of the situation as set forth in ***In re Gardner***, in which the public will have to figure out for themselves just what cancer or virus these compounds are actually useful for. It is very instructive to note that in the entirety of applicants response, applicants are unable to name a specific cancer or virus that the specification teaches can be treated.

Instead, applicants pointed to WO 00/75158. This cannot possibly suffice. The compounds are too different. The WIPO publication is entitled "NOVEL 6-PHENYLPURINE 9-β-D-RIBONUCLEOSIDES". These compounds have at the 6-position a

mandatory phenyl ring with up to three optional substituents. These substituents do not include applicants' amino acid or anything even similar (i.e. do not include amino or acid as a substituent on an alkyl). In fact, applicants aren't even required to have a 6-phenyl group at all, and indeed most compound claims i.e. 2, 3, 5-8 don't even permit a phenyl!!

Further, the compounds of the reference are ribonucleosides. Applicants compounds are not required to be ribonucleosides. Indeed, the great majority of the species in the instant specification were not ribonucleosides.

In addition, it is by no means clear that the compounds of this reference actually are effective for the treatment of any form of cancer. So far as the examiner is aware, none of these compounds from the WIPO publication have ever been themselves established as effective, or indeed, even tested clinically.

To this, applicants presented in the response after final three arguments:

A. "the specification is replete with examples of compounds containing phenyl groups." True, but it is the claims which must be enabled. For claim 2, which cannot have phenyl group at the 6-position (i.e. has n=0), a reference which is limited to compounds which must have a phenyl group at the 6-position is irrelevant.

B. "in fact, the present claim 2 has been amended to explicitly recite a phenyl group." This is confused. The phenyl at the 6-position corresponds to A=phenyl, n=1. The proposed amendment to claim 2, and now, the present claim 2, would not have put that material into claim 2, and even if it had, that would be irrelevant to claim 3 etc.

C. Applicants argue in the middle of page 11 of the response after final that this reference (and also the newly cited Capek reference) teach how to make the compounds, but the enablement rejection here is in terms of how to use the compounds, not how to make the

compounds. Also, the Cepak reference is later than the filing date and hence cannot be relied upon to establish enablement. Further, the examiner must point out that Capek does not teach any utility.

In the response of 12/2/2008, applicants again point to WO 00/75158, saying, "The present application further cites, for example, PCT Publication No. WO 00/75158, as evidence of the many reports of the well-known utility of purine compounds as anti-cancer agents, see page 1, line 10 in the originally filed application."

But that overstates both what the specification has, and what the reference has. First, specification says nothing about "many reports"; WO 00/75158 is the only reference pointed to. Second, the reference does not provide a general teaching of "purine compounds as anti-cancer agents". It only provides a teaching as to the compounds invented in WO 00/75158. Applicants cannot reply on WO 00/75158 for material which is simply not in WO 00/75158. For example, the compounds of WO 00/75158 are ribonucleosides. The reference does not teach anything about compounds which are not ribonucleosides. No claim is limited to ribonucleosides. Most compound claims i.e. 2, 3, 5-8 don't permit a phenyl at the 6-position, but WO 00/75158 is limited to compounds which must have a phenyl. And most importantly, applicants have the mandatory -YmC(optionally protected amino)COOR1 substituent which the reference does not provide for. Applicant's argument concerning the reference has been constructed without regard to what the reference actually has.

And finally, as noted above, apparently none of the reference's compounds have ever been themselves established as effective, or even tested clinically. And in addition to all the above, the specification does not say that the compounds here have efficacy against the same cancers as are named in WO 00/75158.

Applicants earlier stated, "The Examiner has provided no evidence directly contradicting these findings." These findings that applicants refer to are not data on applicants compounds. This is data, of a very preliminary nature, on compounds which have features (6-phenyl, 9-sugar) which applicants are not required to have, and in fact, most of applicants actual species have neither feature.

Applicants earlier continued, "For instance, the Examiner has provided no evidence or data or information which would lead one of skill in the art to not believe the asserted utility of the presently claimed invention." Similarly, in the remarks of 12/2/2008, applicants state: "Applicants further submit that the Examiner has not provided sufficient reasons that would cause a skilled artisan to doubt Applicants' assertion." The examiner's disbelief, or reason to doubt, however, is not the issue here. The problem is that it will take undue experimentation to enable these compounds, owing, as noted above, to the lack of a teaching of specific cancers or viruses, lack of dosage data, lack of any working examples drawn to use, and the staggering size of the genus. The examiner is not stating that he disbelieves the statement in the specification. The examiner is stating that the statement is insufficient to provide an enabling utility without undue experimentation.

On page 13 of the remarks of 4/30/2008, applicants stated, "The Examiner has failed to specify whether the rejection is based on failure to disclose a specific utility, a substantial utility, or a credible utility. It seems that perhaps the Examiner is referring to a lack of credible utility." The problem, as was set forth in the First Action on the Merits, is that it would require undue experimentation to enable the compounds. The issue is not one of credibility.

Indeed, in addition to ***Gardner*** and ***Vaeck***, attention is called to ***In re Schmidt and Wilhelm***, 153 USPQ 640. Treatment of problems with the functioning of a specific body organ, without an indication of which functions are the problem, was held not comply with the enablement requirement, because it simply covered too many different things. The claimed sulfonamide according to the specification "assists the liver function in hepatic disturbances". But, as the decision notes, "the specification contains no specific disclosure as to just how the compound is to be used", so that the specification didn't say which of the many liver functions was intended. Appellants there, as here, point to an outside reference. This reference, "Eger", teaches that certain sulfonamides "may protect the liver against damage from hepatitis and chemical attack by allyl alcohol. Appellants are of the view that the Eger article demonstrates that one skilled in the art would be knowledgeable in the manner of using the present sulfonamide." This argument is essentially the same as what applicants are now arguing with regard to WO 00/75158. But the argument did not avail. The Court noted, "appellants' specification makes no reference to protecting the liver against necrotic changes, and the compounds mentioned by Eger are quite different in structure from that claimed here." The same is true here on both points. The decision continues: "Under the circumstances, it seems to us unduly speculative to assume that, merely because certain apparently unrelated prior art sulfonamides have been used to protect the liver from the adverse effects of hepatitis or chemical attack, one skilled in the art would immediately recognize that the present compound could be used in that manner. It is not clear how appellants determined that their compound has liver assisting activity unless they actually used the compound against certain liver ailments or else depended on unfounded speculation." That is again true in this case, as the specification, as noted above,

contains no biological data of any kind. Thus, applicants use of the WO 00/75158 reference is not consistent with this decision.

In the response after final, applicants stated, "Applicants wish to point out to the Examiner that what is being sought to be patented is not a method of use. Rather, Applicants seek a patent coveting the claims of the present invention, which are directed to compounds, not viruses, cancers, or treatment thereof." The examiner is aware of this and said so explicitly in the previous action. However, all claims must be enabled, regardless of type. The only difference between enablement of compounds and enablement of methods of use is that methods must be enabled for the scope of methods recited in the claim, while the compounds need only a single utility to be enabled. Thus, while applicants say, "Applicants' claims are not directed to any cancers or viruses", those two items, alone with the vague "intermediate", is all that the specification teaches as the use of the compounds. But there must be that utility. Applicants attention is against directed to ***In re Gardner, Roe, and Willey***, 166 USPQ 138, claims 1 and 2, and to ***In re Vaeck***, 20 USPQ2d 1438, claim 1, in which the composition of matter (not method) claims were held to lack enablement because they lacked an enabling utility. Applicants cannot brush aside the enablement requirement in terms of how to use simply because the claims are not method claims.

In the response filed 12/02/2008, applicants state, "If a statement of utility in the specification contains within it a connotation of how to use, 35 U.S.C. 112 is satisfied" and cites case law. But the specification must have more than a "connotation", it must provide a utility which can be put into effect without undue experimentation. Thus, In re JOHNSON, 127 USPQ 216 had utility as an insecticide or fungicide, and the Court noted

correctly that such a use does not require knowledge of "the particular kinds of insects or fungi to be treated" --- since e.g. fungicides are applied without knowledge of what kind of fungus is involved. Exactly the opposite is true for drugs to treat cancer or a virus. Applicants cite In re Brana, 34 USPQ2d 1436, but that case had a very narrow genus, compounds which were extremely close in structure to compounds of established effectiveness, and taught to be better than those, and actual data, none of which is present in this case. Applicants point to In re Hitchings, 144 USPQ 637, but that case not only had a narrow category, acute leukemia, but also the "the inhibition of lactic acid bacteria", as well as test data. The case actually turned on the evaluation of the test data (in mice), a factor not at all relevant here, and thus that case also had a very different fact situation. Applicants also point to In re Bundy, 209 USPQ 48, but that case had a very specific property disclosed: the compounds, which were prostaglandins, were taught to have prostaglandin-like activity, and to be used in the same manner as PGE compounds, which the specification listed as for example, decreasing blood pressure and inhibiting gastric secretion. These are very specific uses, and the decision turned on whether the compounds would actually be expected to have those properties. Thus that case too also had a very different fact situation.

With regard to Gardner, applicants in remarks of 12/2/2008 state, "In ***In re Gardner***, the claims were directed to compositions having an antidepressant activity. Correct; the ***Gardner*** claims were drawn to a composition of matter said to have antidepressant activity. The claims here are drawn to compositions of matter said to have anticancer or antiviral activity (and synthesis thereof), and hence the two situations are quite parallel. In

Garnder, there as only one utility disclosed, so if the compounds lacked that one, they were not enabled.

In the response after final, and again in the response of 12/2/2008, applicants argued, with regard to claims 9-12, that these are method of making claims. Correct, but a method of making a compound is not enabled if there is no enabling utility for the compound itself. See Brenner v. Manson, 383 U.S. 519, 148 USPQ 689. Therefore, it is proper to include claims 9-12 in the rejection, because if the compounds are not enabled, neither is the method of making the compounds.

Applicants earlier discussed the standards for a rejection under 35 USC § 101. No rejection under that statue has been made.

Claim Objections

Claim 2 is objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form. Applicants have narrowed the R'-R" combined choice to provide that NR'R" combined is diphenylmethylimino. But Claim 2 provides that R6 and R7 are optionally substituted phenyl. This is inconsistent, as claim 1 does not provide for the optionally substituted choice. Hence claim 2 is improperly dependent on claim 1.

All claims are drawn to the same invention claimed in the application prior to the entry of the submission under 37 CFR 1.114 and could have been finally rejected on the grounds and art of record in the next Office action if they had been entered in the application prior to entry under 37 CFR 1.114. Accordingly, THIS ACTION IS MADE

FINAL even though it is a first action after the filing of a request for continued examination and the submission under 37 CFR 1.114. See MPEP § 706.07(b). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to /Mark L. Berch/ whose telephone number is 571-272-0663. The examiner can normally be reached on M-F 7:15 - 3:45.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James O. Wilson can be reached on (571)272-0661. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Mark L. Berch/
Primary Examiner
Art Unit 1624

1/3/2009